IN THE SPECIFICATION

Replace the paragraph that begins on page 2, line 2, with the following rewritten paragraph:

A1

It was found in accordance with the present invention that adenosine A3 receptor agonists (A3RAg) activate natural killer (NK) cells and that this activation was abolished in the presence of adenosine A3 receptor antagonists (A3RAn).

Replace the paragraph that begins on page 3, line 15, with the following rewritten paragraph:

A2

Further, the invention provides a method for treatment of a disease comprising administering to an individual in need of such treatment NK cells *a priori* activated with an effective amount of A3RAg. Typically, such a method comprises withdrawing NK cells from the individual, and exposing such cells to an effective amount of at least one A3RAg. Alternatively, the NK cells may also be from a donor individual. Such donated NK cells may be withdrawn after activation with the ~~A3Rga~~ A3RAg in the donor individual or activated *in vitro* after withdrawal and before administering to the recipient individual.

Replace the paragraph that begins on page 5, line 4, with the following rewritten paragraph:

A3

In accordance with a first of its aspects, the present invention provides a method for activating natural killer (NK) cells in an individual, by ~~administer~~

A3 concld'

administering to said individual ~~with~~ an effective amount of one or more A3RAg.

Replace the paragraph that begins on page 5, last line, with the following rewritten paragraph:

A4

- - **Y** represents an oxygen~~,~~ or sulfur ~~of carbon~~ atom or CH_2;

Replace the paragraph that begins on page 6, line 20, with the following rewritten paragraph:

A5

- - $\mathbf{R_4}$ is a hydrogen atom or a group selected from alkyl, substituted alkyl or aryl-NH-C(Z)-, with **Z** being O, S, or NR^a with $\mathbf{R^a}$ having the above meanings; wherein when R_4 is hydrogen ~~than~~ then

Replace the paragraph that begins on page 7, line 7, with the following rewritten paragraph:

A6

or when $\mathbf{R_4}$ is an alkyl or aryl-NH-C(Z)-, then, $\mathbf{R_5}$ is selected from the group consisting of heteroaryl-NR^a-C(Z)-, heteroaryl-C(Z)-, alkaryl-NR^a-C(Z)-, alkaryl-C(Z)-, aryl-NR-C(Z)- and aryl-C(Z)-; **Z** representing an oxygen, ~~sulfor~~sulfur or amine;

Replace the paragraph that begins on page 7, line 15, with the following rewritten paragraph:

A7

wherein $\mathbf{X_1}$, $\mathbf{R_2}$ and $\mathbf{R_4}$ are as defined, and physiologically acceptable salts of said compound.

Replace the paragraph that begins on page 8, line 1, with the following rewritten paragraph:

A8

The non-cyclic carbohydrate groups (e.g. alkyl, alkenyl, alkynyl, alkoxy, aralkyl, alkaryl, alkylamine, etc.) forming part of the substituent of the compounds of the present invention are either branched or ~~unbrancehd~~unbranched, preferably containing from one or two to twelve carbon atoms.

Replace the paragraph that begins on page 8, line 5, with the following rewritten paragraph:

A9

When referring to "***physiologically acceptable salts***" of the compounds employed by the present invention, it is meant any non-toxic alkali metal, alkaline earth metal, and ammonium salts commonly used in the pharmaceutical industry, including the sodium, potassium, lithium, calcium, magnesium, barium, ammonium and protamine zinc salts, which are prepared by methods known in the art. The term also includes non-toxic ***acid addition salts***, which are generally prepared by reacting the compounds of this invention with a suitable organic or inorganic acid. The acid addition salts are those which retain the biological effectiveness and qualitative properties of the free bases and which are not toxic or otherwise undesirable. Examples include, *inter alia*, acids derived from mineral acids, hydrochloric, hydrobromic, sulfuric, nitric, phosphoric, metaphosphoric and the like. Organic acids include, *inter alia*, tartaric, acetic, propionic, citric, malic, malonic, lactic, fumaric, benzoic, cinnamic, mandelic, glycolic, gluconic, pyruvic, succinic, salicylic and arylsulphonic, e.g., p-toluenesulphonic, acids.

Replace the paragraph that begins on page 8, line 19, with the following rewritten paragraph:

Specific examples of A3RAg which may be employed according to general formula (IV) of the present invention include, without being limited thereto, N^6-2-(4-aminophenyl)ethyladenosine (APNEA), N^6-(4-amino-3-iodobenzyl) adenosine-5'-(N-methyluronamide) (AB-MECA) and N^6-(~~2~~3-iodobenzyl)-adenosine-5'-N-~~methlyuronamide~~ methyluronamide (IB-MECA) and preferably 2-chloro-N^6-(~~2~~3-iodobenzyl)-adenosine-5'-N-methyluronamide ~~methlyuronamide~~ (Cl-IB-MECA).

A10

Replace the paragraph that begins on page 9, line 7, with the following rewritten paragraph:

Further, provided by the present invention is a method for treatment of a disease comprising administering to an individual in need of such treatment NK cells *a priori* activated with an effective amount of A3RAg. In accordance with one embodiment, the NK cells are autologous cells *a priori* withdrawn from the same individual and then activated *ex vivo* by contacting them with an amount of an A3RAg effective to activate them, and then reintroduced to the individual, by a suitable parenteral administration. Alternatively, the NK cells may at times be obtained from a donor individual either after activation *in vivo* by administering the A3RAg to the donor individual a sufficient time prior to withdrawal of the cells, or activating the cells *ex vivo* as above, or both. Methods for withdrawal of

A11

A11 concld

relatively purified NK ~~cells~~ cell populations from an individual and their *ex vivo* culture are known in the art and need not be further elaborated herein.

Replace the paragraph that begins on page 9, line 24, with the following rewritten paragraph:

A12

When providing A3RAg to an individual for *in vivo* treatment or to an animal model for *ex vivo* treatment, it is preferably formulated for oral delivery. However, other methods of administration are also suitable such as parenteral administration including intravenous, subcutaneous, intramuscular and intramedullary injection, intraarterial, ~~intraperitoneally~~ intraperitoneal and intranasal administration, as well as ~~intrathecal~~ intrathecally and by infusion techniques. For oral administration, A3RAg with good oral bioavailability may preferably be chosen. Screening for an ~~A3Rag~~ A3RAg with good oral bioavailability and good effectivity in achieving the desired therapeutic effect, is a routine task within easy reach of the artisan.

Replace the paragraph that begins on page 10, line 13, with the following rewritten paragraph:

A13

It is noted that humans are treated generally longer than experimental animals as exemplified herein, which treatment has a length proportional to the length of the disease process. The doses may be single doses or multiple doses over a period of time, e.g. several days and may depend ~~of~~ on physical characteristics such as the ~~high~~height, weight,

and gender of the individual to be treated. Generally, the ~~administrated~~ administered doses are preferably unit dosage form. The treatment generally has a length which may be contingent on the length and stage of the disease process and active agent effectiveness and the patient species being treated.

A13 concl'd

Replace the paragraph that begins on page 10, line 25, with the following rewritten paragraph:

By the term ***"pharmaceutically acceptable additives"*** it is meant any inert, non-toxic materials, which do not react with A3RAg and which are typically added to formulations as diluents or carriers or to give form or consistency to the formulation, to give it a specific form, e.g. in pill form, as a simple syrup, aromatic powder, and other various forms. The additives may also be substances for providing the formulation with stability (e.g., preservatives) or for providing the formulation with an edible flavor, etc.

A14

Replace the paragraph that begins on page 11, line 14, with the following rewritten paragraph:

Accordingly, pharmaceutical compositions suitable for oral administration may consist of (a) liquid solutions, where an effective amount of A3RAg is dissolved in diluents, such as water, saline, natural juice, alcohols, syrups, etc.; (b) capsules (e.g. the ordinary hard- or soft-shelled gelatin type containing, for example, surfactants, lubricants, and inert fillers), tablets, lozenges (wherein A3RAg is in a

A15

flavor, such as sucrose and acacia or tragacanth, or the A3RAg is in an inert base, such as gelatin and glycerin), and troches, each containing a predetermined amount of A3RAg as solids or granules; (c) powders; (d) suspensions in an appropriate liquid; (e) suitable emulsions; (f) liposome formulation; and others.

A15 concl'd

Replace the paragraph that begins on page 12, line 1, with the following rewritten paragraph:

Pharmaceutical compositions formulated for parenteral administration may include aqueous and non-aqueous, isotonic sterile injection solutions, which can contain anti-oxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. Oils, such as petroleum, animal, vegetable, or synthetic oils, and soaps, such as fatty alkali metal, ammonium, and triethanolamine salts, and suitable detergents may also be used for parenteral ~~administrtion~~administration. Further, in order to minimize or eliminate irritation at the site of injection, the compositions may contain one or more nonionic surfactants. Suitable surfactants include polyethylene sorbitan fatty acid esters, such as sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base,

A16

A16 concl'd

formed by the condensation of propylene oxide with propylene glycol.

Replace the paragraph that begins on page 13, line 2, with the following rewritten paragraph:

A17

The effect of the A3 adenosine receptor agonist 2-chloro-N^6-(~~2~~3-iodobenzyl)-adenosine-5'-N-~~methly-uronamide~~methyluronamide (Cl-IB-MECA)~~.~~, on the *in vitro* and *in vivo* activity of NK cells, was tested.

Replace the paragraph that begins on page 13, line 6, with the following rewritten paragraph:

A18

In this set of experiments, the effect of the synthetic adenosine A3 receptor agonist (~~A3ARAg~~A3RAg), 2-chloro-N^6-(3-iodobenzyl)-adenosine-5'-N-methyl-uronamide (Cl-IB-MECA) on the activity of murine ~~spleenocytes~~splenocytes or human peripheral blood mononuclear cells was tested.

Replace the paragraph that begins on page 13, line 10, with the following rewritten paragraph:

A19

The A3 adenosine receptor antagonist 9-chloro-2-(2-furanyl)-5-[(phenylacetyl)amino][1,2,4,]-triazolo[1,5-c] quinazoline (MRS-1220) was used to prove the specific binding of Cl-IB-MECA to the ~~A3ARA~~3R.

Replace the paragraph that begins on page 13, line 19, with the following rewritten paragraph:

A20

The effect of Cl-IB-MECA on the activity of human peripheral blood NK cells was assayed by a standard 4h ^{51}Cr-release assay using K562 leukemia cells as targets.

A20

Splenocytes or human mononuclear cells were cultured at a concentration of $5x10^5$ cells/well in 96 well round bottom plates, and used as the effector (E) cells. The cells were preincubated with 10 nM Cl-IB-MECA for 18 hours, then the agonist was washed out from the wells and the cells were re-suspended in RPMI containing 5% FCS. K562 cells were used as the targets (T) and were labeled with 100 μCi~~μci~~ of $Na_2[^{51}Cr]O_4$ at 37°C, for 1 hr.

Replace the paragraph that begins on page 15, line 20, with the following rewritten paragraph:

A21

In another experiment, the capability of the *"activated"* splenocytes to act *in vivo* against melanoma cells was examined. The *"non-activated"* and *"activated"* splenocytes were engrafted to mice that were inoculated 4 days earlier with B-16 melanoma cells ($2.5x10^5$). ~~As the control served mice~~Mice that were inoculated with the B-16 melanoma cells ~~however~~ but not engrafted with splenocytes served as the control.